REMARKS

The Office action of April 28, 2008 has been carefully reviewed. The Applicants noted that claims 2, 4, 7, 9, 23 and 25 were objected to under 37 CFR 1.75(c) and all pending claims were rejected under 35 USC 112, the first paragraph for lack of enablement.

The Examiner's objection to claim forms under 37 CFR 1.75(c) is well taken and corrections have been made by amendments and canceling of the objected claims. It is respectfully submitted that the claims as presently amended have overcome the objection.

The Applicant respectfully disagrees with the rejection made under 35 USC 112, the first paragraph for the reasons stated in the following.

The Invention

The present invention relates to a sensitive method for detecting colorectal cancer, particularly at an early stage. The method is based on the measurement of the blood level of beta-catenin associated RNA, DNA, or both because it is demonstrated that these beta-catenin associated nucleic acids can be clearly detected in all the patients tested while they are not detectable (or detected at a significantly lower level) using the measurement methods under the particular conductions disclosed herein. This method is simple with high degree of accuracy, requiring small volumes of blood sample, which can be obtained by non-invasive, normal blood-drawing procedures. The measurement of blood level of the nucleic acid encoding for the protein beta-catenin was well development and within ordinary skill of a person working in this art when the invention was made. The validity and operability of the method of the present invention was confirmed by a subsequently published paper (Wong et al, Clinical Cancer Research, Vol. 10, 1613-1617, March 1, 2004).

The Rejection under 35 USC § 112, the first paragraph

In making this rejection, the Examiner noted that "the detection of RNA and DNA is well established. However, the association of particular DNA and RNA levels or sequences with a particular disease is not routine." The Applicant agrees with the Examiner in that the association of particular DNA and RNA levels or sequences with a particular disease is not routine. That is why the present invention was needed to make the association. The present invention was about the association between the blood level of beta-catenin associated nucleic acids and a particular disease, namely, colorectal cancer. The data obtained in the present invention and disclosed in the present specification undoubtedly demonstrated such association. People with ordinary skill in the art could readily appreciate the association by reading the present specification. This association was also subsequently confirmed by the Wong reference.

Apparently, the Examiner's rejection of the present application for lack of enablement is not based on the ground that people with ordinary skill in the art is unable to perform the necessary procedure of the claimed method to obtain the data. Nor is it based on the ground that the data disclosed in the present specification cannot demonstrate the association between the blood level of beta-catenin associated nucleic acids and a particular disease. Instead, the rejection is apparently grounded on the Examiner's own belief that the claimed invention cannot work as taught by the specification. Such belief is based on an erroneous understanding and interpretation of a subsequent publication: Wong et al, (*Clinical Cancer Research*, Vol. 10, 1613-1617, March 1, 2004) and further based on irrelevant citation of the facts from Osman et al (*Clin Cancer Res.* Vol. 12, No. 11, June 2006) and Fleischhacker et al. (*Biocheimica et Biophysica Acta*, Vol. 1775, 2007).

As discussed in the following, the rejection based on such ground is erroneous both as a matter of law and as a matter of specific facts in this case.

The 112 Rejection is erroneous as a matter of law

As discussed above, in making the 112 rejection, the Examiner made no attempt to suggest that (i) people with ordinary skill in the art is unable to perform the necessary procedure of the claimed method to obtain the data or (ii) that the actual data disclosed in the present specification cannot demonstrate the association between the blood level of the beta-catenin associated nucleic acids and a particular disease, namely, colorectal cancer. In fact, the Examiner, or anyone else with ordinary skill in the art, cannot dispute that the following actual data obtained in the present invention provided a clear association between the biomarker (beta-catenin related nucleic acids) and the disease (colorectal cancer):

Subjects	β -catenin mRNA (range) (copy)	β-catenin mRNA (median) (copy)
Carcinoma	6,700-44,000	22,000
Adenoma	690-1800	1,100
Normal	0-169	36

Under this circumstance, the claimed invention of the instant application is *prima facie* enabled unless the Examiner can present evidence indicating that the above data is not trustworthy, either improperly or incorrectly obtained. In the instant case, the Examiner did not, and cannot, suggest that the above data is untrustworthy or is unbelievable.

Instead, the Examiner cited the Wong, Osmer and Fleischhacker references to advance an argument that the present invention is in an "unpredictable art".

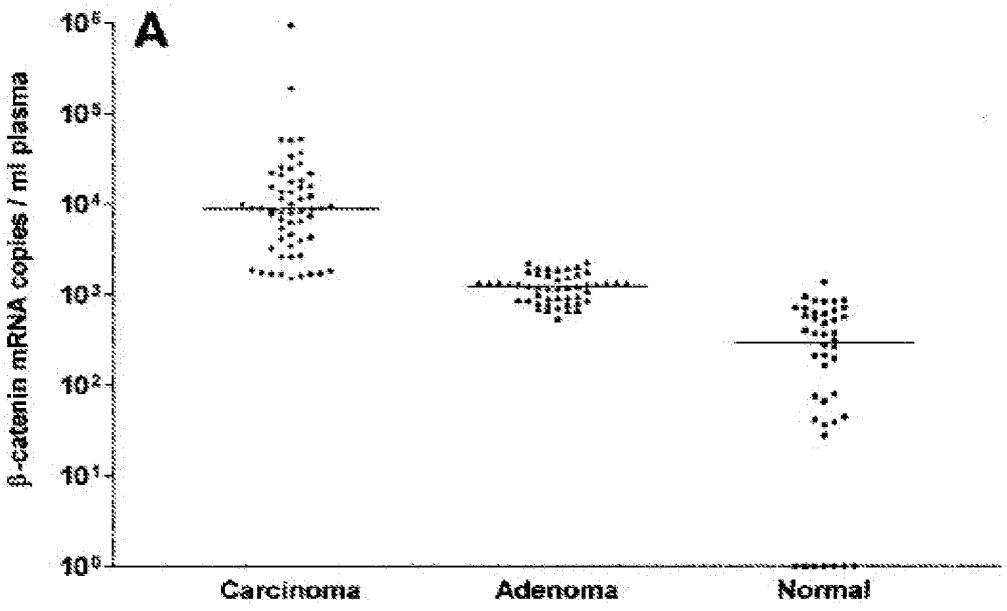
Even if the cited references prove that the present invention is in an unpredictable art, it is erroneous as a matter of law to reject the claimed invention simply because it relates to an unpredictable art. The law does not equal unpredictability with non-enablement.

It is respectfully submitted that in the cases where, as it is here, the invention description itself is *prima facie* enabling, the claims cannot be rejected for lack of enablement based on other art references unless those other references present evidence indicating that the description by the inventor is untrustworthy or unbelievable, like a description of a perpetual machine. The Examiner did not and cannot make such allegation in the instant case and thus the rejection under 35 USC section 112, the first paragraph, must be set aside as a matter of law.

The 112 Rejection is erroneous as a matter of facts

(A) The Wong reference supports the present invention

Much of the Examiner rejection is grounded on the Wong reference. Apparently, the Examiner believes that the Wong reference is significantly inconsistent with the data obtained in the present invention. It is a misreading of the Wong reference. The Wong reference not only does not discredit the data of the present invention, but provides a forceful support to the present invention: measuring the blood level of beta-catenin mRNA is a good tool for detecting colorectal cancer. It is reliable. It is valuable. This is an undisputable fact clear to anyone with ordinary skill in the art in view of the following data disclosed in the Wong reference:



To put the data in the numerical format, the Wong reference disclosed the beta-catenin mRNA range and median for people with carcinoma, people with ademona and normal people, respectively, as following:

Subjects	β -catenin mRNA (range) (copy)	β-catenin mRNA (median) (copy)
Carcinoma	1,480-933,100	8,737
Adenoma	541-2,254	1,218
Normal	0-1,366	291

These data unambiguously verify the operability and value of the claimed method of the present invention: detecting the possible presence of carcinoma by measuring beta-catenin associated RNA in the blood.

(B) <u>The cited art references are misunderstood or misused</u>

In a medical measurement, present or absence of a substance is generally used in a relative sense and the threshold between presence and absence can be predetermined and preset according to the particular situation, sensitivity of detection tools and current knowledge of all relevant issues. For example, one with ordinary skill in art, in view of the above data, may decide the baseline or threshold to be set at 540, above which the measurement would indicate presence of an abnormal amount of beta-catenin mRNA and need for more invasive check for possible presence of adenoma and carcinoma. Even when setting the threshold at this level, the method is valuable because most normal people (as the median is 291) would avoid more invasive procedures. Thus, whether beta-catenin mRNA is detectable in most normal persons is not an issue. The issue is whether its level is sufficiently varied among groups of people with different conditions. Both the present invention and the Wong reference unambiguously demonstrated that beta-catenin RNA level is sufficiently different in three different groups of people to have a diagnostic or assessment value, notwithstanding the overlapping measurement ranges between

the different groups. Therefore, the fact that beta-catenin mRNA is present in most normal people and the fact the different groups of people have overlapping ranges of beta-catenin mRNA do not support the Examiner's contention that the present invention as claimed is not enabled.

Similarly, a method claim enabled within the meaning of patent law doesn't mean it doesn't need further refinement to become more useful or for more applications. Yes, the Wong reference called for a more intensive study necessary to explore the applicability of the present claimed invention for prognostic use and called for a large-scale study to decide whether the present invention can be applied to population screening. But, a patent claim cannot be rejected for lack of enablement because it can be, with more studies, extended to further applications. In fact, many so-called "dominant" patent claims can encompass additional subsequent patents claiming refinements and further applications of the basic idea of the dominant patent.

(C) The Osmer and Fleischhacker references are irrelevant

It is simply unclear to the Applicant what is the relevance of the Osmer and Fleischhacker references to the enablement issue in the instant issue. Neither reference says anything about whether one with ordinary skill in the art is unable to measure the level of the beta-catenin related nucleic acids in the blood using a method taught by the present invention, nor anything about whether one with ordinary skill in the art is unable to appreciate the correlation between the measured level of beta-catenin related nucleic acids and the presence of possible colorectal cancer.

It is respectfully submitted that even if in the situation where an art reference does actually contradict the idea of the claimed invention (which is not the case here), an examiner cannot simply use the teaching of the reference as the basis to reject the claimed invention as unenabled, as if only the cited reference speaks the truth when in conflict with the claimed invention. Without more facts or reasoning, the examiner is in no position to judge which one, reference or instant specification, is trustworthier.

Conclusion

In view of the foregoing remarks, the Applicant respectfully submits that the rejection under 35 USC section 112, the first paragraph in this case was improper both as a matter of law and as a matter of facts. The claims as presently amended should be allowed.

Respectfully submitted,

George G. Wang, Ph.D., Reg. No.: 41,419
Attorney for Applicant

Dated June 27, 2008

Wilkinson & Grist
6th Floor, Prince's Building
Charter Road, Hong Kong

Telephone (852) 2905-4786
Telefax (852) 2520-2090